Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-131 are pending in this application and are rejected on various grounds. Claim 128 has been canceled without prejudice or disclaimer. Claims 119-124 have been amended with the functional recitation: "wherein, the nucleic acid encoding said polypeptide is amplified in lung adenocarcinomas." Claim 130 has been amended for proper claim dependency. The rejections to the presently pending claims are respectfully traversed.

Specification

The disclosure was objected to by the Examiner as containing "browser-executable code." The foregoing amendment to the specification which deleted all embedded URLs is believed to overcome the present objections.

In addition, amendments to the specification have incorporated the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Accordingly, Applicants believe that all objections to the specification has been overcome.

Continuity

The Examiner asserts that Applicants haves not complied with conditions to receive benefit of an earlier filing date under 35 U.S.C. 119(e) because allegedly, the provisional applications listed in the first paragraph of the instant application do not refer to SEQ ID NO: 357, PRO1182 or Figure 252. Applicants respectfully traverse.

Applicants submit that they rely on the gene amplification assay for patentable utility of PRO1182 and its antibodies, which was first disclosed in U.S. Provisional Application 60/141,037, filed June 23, 1999, priority to which has been claimed in this application. Applicants note that the sequences disclosed in the U.S. Provisional Application 60/141,037 have a different sequence listing and a different Figure numbering from that of the current application; therefore, the sequence of PRO1182 is listed as SEQ ID NO: 51, Figure 38 in Application 60/141,037. Hence, Applicants are entitled to the benefit of the above provisional application,

and accordingly, to an effective filing date of at least **June 23, 1999.** The Examiner is respectfully requested to reconsider this application's priority based on this clarification.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-131 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility." Claims 119-131 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

The Examiner asserts that no utility for PRO1182 exists even if the specification implies a credible, specific and substantial utility for PRO1182 based on structural identity and quotes exemplary articles like Skolnick *et al.*, Bork *et al.*, Doerks *et al.*, Hesselgesser *et al.*, Blease *et al.* and Wu *et al.*, to show that "function cannot be predicted based solely on structural similarity to a protein found in sequence databases." Applicants respectfully disagree with and traverse these rejections.

Utility Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must

be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Arguments

Initially, Applicants submit that an assertion for utility of PRO1182 is not based on structural similarity. Applicants add that the articles cited by the Examiner that discuss utility based on structural similarity, namely, Skolnick *et al.*, Bork *et al.*, Doerks *et al.*, Wu *et al.* and Hesselgesser *et al.*, have no bearing on the issue of utility. In the present case, Applicants have shown experimentally that the DNA encoding for PRO1182 is amplified in human lung

adenocarcinomas and rely on this data for patentable utility of the PRO1182 polypeptide and its antibodies for the diagnosis of human lung adenocarcinomas.

Gene amplification is an essential mechanism for oncogene activation and the assay is well-described in Example 170, page 539 of the present application. The gene amplification data shows that genomic DNA was isolated from a variety of primary cancers and cancer cell lines listed in Table 9 (especially page 554, Table 9C) which includes primary lung cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29). Gene amplification was monitored using real-time quantitative TaqMan™ PCR and the results are set forth in Table 9A. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9C indicates that PRO1182 showed approximately 1.43-1.81 ΔCt units which corresponds to $2^{1.43}$-$2^{1.81}$- fold amplification or **2.694 fold to 3.506-fold** amplification in lung tumors, which is significant and thus the PRO1182 gene has utility as a diagnostic marker of human lung adenocarcinomas.

Applicants further submit that it is generally well-understood in the art that DNA copy number influences gene expression. For example, Ornfoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Ornfoft *et al.* showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack *et al.*, who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is

associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that gene amplification correspondingly increases mRNA expression, in general.

Also enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of amplified genes, the combined teachings in the art exemplified by Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*, and the Polakis declaration overwhelmingly teach that gene amplification influences gene

expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the amplification data for the PRO1182 gene, that the PRO1182 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1182 proteins and its antibodies have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules.

Claimed proteins would have diagnostic utility even if the protein were not overexpressed

Even assuming *arguendo* that, there is no correlation between gene amplification and increased mRNA/protein expression for PRO1182, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with

agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1182 polypeptide, for example, in detecting over-expression or absence of expression of PRO1182 in lung adenocarcinomas. The art clearly indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. The skilled artisan would not require undue experimentation to make and use the claimed invention because methods for obtaining such variants are well-described throughout the instant specification, at least on page 305, last paragraph. Thus, Applicants request reconsideration and that the present rejections under 35 U.S.C. §101 and §112, first paragraph rejections be withdrawn.

Claim Rejections – 35 USC § 112, first paragraph- Written Description

Claims 119-131 are also rejected under 35 U.S.C. 112, first paragraph because, according to the Examiner, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing." Further, the Examiner contends that "the specification teaches a polypeptide (SEQ ID NO: 357) but does not teach functional or structural characteristics of all claimed polypeptides. The description of one PRO polypeptide (SEQ ID NO: 357) is not adequate written description of an entire genus of functionally equivalent polypeptides." Applicants respectfully traverse this rejection.

The Legal standard for Written Description

The well- established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *In re* Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F. 2d at 1563, 19 USPQ2d at 1116 (Fed. cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. see e.g.Vas-Cath, Inc. v. Mahurkar, 935 F. 2d at 1563, 19 USPQ2d at 1116 (Fed. cir. 1991). The factual determination in a written description analysis depends on the **nature of the invention** and **the amount of knowledge imparted to those skilled in the art by the disclosure.** Union Oil v. Atlantic Richfield Co., 208 F. 3d 989, 996 (Fed. Cir. 2000).

Arguments

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The instant invention, defined by the claims, concerns polypeptides having 80%, 85%, 90%, 95% or 99% sequence identity with the disclosed polypeptide sequence SEQ ID NO: 357 with the functional recitation: "wherein the nucleic acid encoding said polypeptide is amplified in lung adenocarcinomas." The present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. Based on the detailed description of the cloning and expression of variants of PRO1182 in the specification, the description of the gene amplification assay and description of testing the ability of test variant polypeptides in the assay, the actual reduction to practice of sequence SEQ ID NO: 357 and the functional recitation

in the instant claims, Applicants submit that one of skilled in the art would know that Applicants possessed the invention as claimed in the instant claims.

Hence, Applicants submit that this rejection should be withdrawn.

Claim Rejections – 35 USC § 112, first paragraph- Deposit rules

Claims 119-124 and 129-131 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner contends that the ATCC deposit of the current invention needs the current address of the ATCC and a declaration or statement stating that all restrictions imposed by the depositor on the public be irrevocably removed.

Applicants submit that ATCC deposit No. 203088 was made under the Budapest Treaty, as indicated on page 566 and the address of the ATCC is correct as indicated on page 563, line 10 of the instant specification. Applicants have also added the requisite assurances in instant amendments to the specification that irrevocably remove all restrictions imposed by the depositor on the availability of deposited material to the public upon the granting of the pertinent U.S. patent. Accordingly, this rejection should be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 119-131 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. The Examiner contends that the claims are rendered indefinite because of "the phrase extracellular domain."

Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled references to "extracellular domain" in the claims; that is part (c) and (d) of the claims have been deleted for clarity. Accordingly, Applicants submit that the claims are definite and respectfully request that this rejection be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C33). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: June 23, 2004

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